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June 27, 2005

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition on behalf of the American College of Gastroenterology, pursuant to 21 C.F.R. § 10.30 (2005), to request the Commissioner of Food and Drugs to remove from the labeling for propofol (Diprivan®) the warning that propofol should be administered only by persons trained in the administration of general anesthesia, rather than by other qualified medical professionals.

Substantial clinical evidence establishes that propofol can be administered safely, effectively, and cost-effectively by gastroenterologists and by registered nurses working under their supervision. The requested label change will promote efficiency and reduce costs to payors by eliminating the need for an anesthesiologist or nurse anesthetist to be present to administer propofol during an endoscopic procedure. The requested label change also will eliminate a restriction on the practice of gastoenterologists that, in light of the clinical evidence, is unwarranted.

A. Action Requested

The petitioner requests that the Commissioner of Food and Drugs remove the following warning from the labeling for propofol:

> For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered

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only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure.

B. Statement of Grounds

Propofol has advantages over alternative sedation agents for endoscopic procedures. Restrictions imposed by as many as twelve States and many hospitals, however, increase the costs to payors of using propofol for such procedures. The labeling of propofol specifies that it should be administered "only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure"; *i.e.*, only by anesthesiologists or nurse anesthetists. Consistent with the labeling, some States and hospitals permit propofol to be administered only by anesthesiologists or nurse anesthetists. The result is that an anesthesiologist or nurse anesthetist must be present to administer propofol during an endoscopy, with a resulting increase in the cost of an endoscopic procedure.

A number of controlled and uncontrolled clinical studies have established that propofol can be administered safely and effectively by medical professionals other than anesthesiologists or nurse anesthetists. The warning that propofol should be administered only by anesthesiologists or nurse anesthetists who are not involved in the conduct of the surgical/diagnostic procedure ("Warning"), therefore, now is unwarranted. For this reason, as set forth more fully below, petitioner requests that the Warning be removed.

1. Propofol Is Superior to Alternative Sedation Agents for Endoscopic Procedures.

Propofol has several advantages over alternative sedative agents (benzodiazepines and narcotics) for endoscopic procedures. The alternatives include midazolam (Versed®) and meperidine (Demerol®). In controlled clinical trials, propofol has been found to induce deeper sedation than alternative agents.[1,2,3,*] Propofol induces sedation more rapidly than a midazolam-meperidine or midazolam-fentanyl combination.[1,3] Also, propofol results in faster recovery times than midazolam with meperidine or midazolam with fentanyl.[1,3] Finally, propofol is associated with better post-procedure functioning than alternative sedation agents.[1,3]

Certain risks are inherent in propofol. First, propofol is a cardiovascular depressant drug that causes a drop in blood pressure.[4,5] Second, propofol is a respiratory depressant drug that can lead to partial airway obstruction.[4] Third, the short duration of propofol sedation requires more frequent reinforcing doses, which lead to greater peak levels of sedation and make propofol a more demanding agent to administer than alternative sedation agents.[6] Finally, there is no reversal drug for propofol, so an overdose must be treated with assisted ventilation until the patient's own spontaneous ventilation resumes.[4,7]

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* Copies of cited articles are included in the Appendix accompanying this petition.

Despite these risks, the risk profile of propofol appears to be no worse than that of alternative sedation agents. Qadeer *et al.*[8] concluded from a meta-analysis of controlled studies that propofol sedation for gastrointestinal endoscopy carries a complication profile that is equivalent to that of traditional sedation using a combination of a narcotic and a benzodiazepine. The same authors concluded, in a separate abstract,[9] that propofol sedation is associated with significantly less risk of cardiopulmonary complications than traditional sedation for colonoscopy. Gangi *et al.*[10] reported on a retrospective review of data from nine hospitals in which propofol was associated with a greater risk of cardiovascular complications than alternative sedation agents, but not at a level of statistical significance (p=0.09).

2. The Present Labeling Encourages Unnecessary Cost and Inefficiency When Propofol Is Used for Endoscopic Procedures.

In accordance with the Warning, some States and hospitals require that propofol be administered only by an anesthesiologist or Certified Registered Nurse Anesthetist (CRNA).[11,12,13] Those States and hospitals bar gastroenterologists, and nurses working under their supervision and direction, from administering propofol.

In such States and hospitals, a gastroenterologist must retain an anesthesiologist or nurse anesthetist in order to provide propofol sedation during an endoscopic procedure. The average reimbursement to anesthesiologists for providing sedation during a colonoscopy is $106 from Medicare and approximately $400 from commercial insurers.[13]

Requiring the presence of an anesthesiologist or nurse anesthetist to administer propofol thus substantially increases the cost of an endoscopic procedure. It is inefficient and unnecessary for the cost of an endoscopic procedure to include fees for both a gastroenterologist and either an anesthesiologist or nurse anesthetist, for the reasons set forth in the following section.

3. Substantial Clinical Evidence Establishes that Gastroenterologists and Nurses Working Under their Supervision Can Administer Propofol Safely and Effectively.

A number of recent studies establish that propofol is safe in the hands of gastroenterologists and nurses working under their supervision. The studies show that the safety concerns that underlie the Warning no longer are warranted. Those safety concerns are reflected in the conclusions by some authors[4,14,15] that propofol should be administered only by anesthesiologists, and in a recent abstract from a poster presentation that concludes that the administration of propofol by anesthesiologists is associated with a lower risk of some cardiopulmonary complications than the administration of propofol by medical personnel other than anesthesiologists. In that abstract, Vargo *et al.*[16] reported on a retrospective analysis of such data as could be extracted from the Clinical Outcomes Research Initiative (CORI) database, an endoscopic outcomes database. Definitive conclusions cannot be drawn from the Vargo *et al.* abstract because (i) the database relied on collected a wide range of information, not necessarily

tailored for the specific subject matter and protocol used in this abstract, (ii) the criteria for data collection may not have been consistent across the various reporting centers and medical practices; (iii) one of the authors noted in a conversation (June 2005) that the results are different depending on the type of procedure, and that the analysis did not control for any additional sedation agents administered in conjunction with propofol. The administration of propofol in conjunction with a narcotic, such as fentanyl, can amplify the cardiac and respiratory side effects of propofol.[2,4,5,14] Moreover, (iv) Vargo *et al.* defined cardiovascular complications broadly to include chest pain and other conditions that may not be associated with serious adverse events.[16]

Substantial clinical evidence establishes that medical personnel other than anesthesiologists can safely and effectively administer propofol. Four controlled studies and one analysis of clinical data have concluded that propofol, when administered by gastroenterologists, general practitioners, or registered nurses, has a safety profile comparable to that of alternative sedation agents administered by gastroenterologists or registered nurses.

Vargo *et al.*[17] randomized 75 patients between propofol and meperidine/midazolam. The sedation agent was administered to each group by a gastroenterologist. There was no significant adverse event in the propofol group that resulted in termination of the procedure or temporary ventilatory assistance. Moreover, there was no statistically significant difference between the groups for patients with oxygen saturation levels below either 85% or 90%, or in the need for supplemental oxygen. Changes in systolic blood pressure in the two groups were equivalent.

Sipe *et al.*[1] randomized 80 colonoscopy patients to receive either propofol or a combination of midazolam and meperidine. Both groups received sedation from registered nurses supervised by an endoscopist. There was a single complication in the propofol group: epistaxis, followed by coughing and then transient oxygen desaturation to less than 85% in one patient. The patient responded to an increase in the concentration of inspired oxygen, and mechanical ventilation was not needed. Four patients in the midazolam/meperidine group experienced complications: tachycardia (>125 bpm, n=1), hypotension and bradycardia requiring administration of atropine (n=1), and isolated hypotension (n=2).

Ulmer *et al.*[3] reported on a controlled trial of 100 colonoscopy patients randomized to receive either propofol or a combination of midazolam and fentanyl, conducted by the same group as the Sipe *et al.*[1] study. Registered nurses supervised by an endoscopist administered sedation to both groups. Six minor complications occurred in the propofol group. Four patients experienced hypotension (systolic blood pressure < 90 mm Hg), but all improved without specific treatment. One patient experienced an episode of bradycardia (heart rate < 50 per minute) that responded to atropine. Finally, one patient developed a rash. Five complications occurred in the group receiving midazolam and fentanyl. Four patients experienced hypotension, and one patient had oxygen desaturation to 73% that was resolved with mask ventilation for 30 seconds. The authors noted that they had administered propofol to over

6,000 patients without any need for endotracheal intubation, hospitalization, or resulting in sequelae.

Kongkam *et al.*[18] randomized 75 patients to receive from gastroenterology fellows either midazolam and meperidine (n=34) or propofol (n=41). Fewer patients in the propofol group (n=6) than in the midazolam/meperidine group (n=13) experienced at least one episode of oxygen saturation less than 90% (p=0.019). There were no other statistically significant differences in physiological outcomes.

Vargo *et al.*[19] analyzed data from the CORI database for 9,761 cases of propofol administered during endoscopy by medical personnel other than anesthesiologists, and 528,131 cases of standard sedation and analgesia administered during endoscopy. The authors concluded that the overall risk of cardiopulmonary complications was equivalent.

In addition, thirteen uncontrolled studies have concluded that propofol may be administered safely and effectively by gastroenterologists or registered nurses.

Walker *et al.*[20] reported on 9,152 cases of propofol given by registered nurses under the supervision of endoscopists or gastroenterologists. No patient in that study needed endotracheal intubation, laryngeal mask airway, or rescue by an anesthesiologist. There were seven cases of significant respiratory compromise – three due to apnea (treated with mask ventilation for 30 seconds (n=2) or recovered spontaneously within 30 seconds (n=1)), three due to apparent laryngospasm (all successfully treated with mask ventilation for 30-60 seconds), and one case of aspiration resulting in hospitalization – all occurring during or after upper endoscopy, and not colonoscopy.

Rex *et al.*[21] reported on the safe and effective administration of propofol by registered nurses supervised by gastroenterologists in 2,000 cases. Five patients experienced oxygen desaturation less than 85%. One episode resulted from a coughing paroxysm in a patient undergoing colonoscopy, and was resolved with an increase in inspired concentration of oxygen. The remaining four episodes of oxygen desaturation less than 85% occurred during upper endoscopy, and all four patients were mask ventilated for intervals of less than one minute. There were 11 episodes of oxygen desaturation to less than 90% but greater than 85%. All such patients responded to increased inspired oxygen concentration. Seven of the 11 episodes occurred during upper endoscopy. The authors reported that no patient needed endotracheal intubation, was admitted for observation, or had other long-term sequelae as a result of desaturation. Moreover, no perforation occurred during any procedure.

Rex and colleagues[22] also reported on the safety record of propofol administered by nurses in 28,697 cases at 3 endoscopy centers. Only 42 cases (.14%) needed assisted ventilation. No event led to endotracheal intubation or resulted in death or neurological sequelae.

Tohda *et al.*[23] reported that nurses working under the supervision of endoscopists safely and effectively administered propofol to 25,200 patients over 7 years. Hypoxemia (O_2 saturation <90%) occurred in 6.5% of the patients, and severe hypoxemia (O_2 saturation <85%) occurred in 0.52% of the patients. Oxygen administration through nasal cannulla was necessary in 7.2% of cases. Mask ventilation and endotracheal intubation were not needed in any case. A decline in systolic blood pressure <90 mm Hg was observed in 3.5% of colonscopy cases and 0.7% of upper endoscopy cases, and heart rate less than 50 bpm occurred in 1.7% of cases. These situations were corrected using intravenous saline solution.

Baptista *et al.*[24] reported that propofol was safely and effectively administered by nurses supervised by endoscopists in a study of 7,000 endoscopic procedures. The ventilatory complication rate was 0.12%. There were 8 cases of oxygen desaturation <85% that led to mask ventilation over 1 to 4 minutes. In 1 patient, ventilatory failure occurred during induction for endoscopic retrograde cholangiopancreatography (ERCP), resulting in tracheal intubation and general anesthesia to complete the procedure. No colonic perforations occurred in any procedure.

Heuss *et al.*[25] reported that, in an uncontrolled study, registered nurses had administered propofol safely to 2,574 patients. The authors concluded that the risk profile for nurse-administered propofol was, in fact, better than that previously reported for benzodiazepines. Of the 2,574 patients, 43 (1.7%) experienced hypoxemia, probably induced by propofol sedation. In 37 cases, the hypoxemia lasted less than 1 minute and was reversed by giving the patient additional oxygen. Intervention was necessary in the remaining 6 cases (0.2%): insertion of a nasopharyngeal tube (n=3) or manual mask ventilation (n=3) for less than 2 minutes. All patients recovered without sequelae. A decrease in systolic blood pressure below 90 mm Hg occurred in 379 patients (14.6%), but was corrected by saline solution infusion, with no sequelae. Bradycardia, probably related to sedation, occurred in 95 patients (3.7%).

Yusoff *et al.*[26] reported that endoscopists administered propofol safely and effectively to 500 patients in an uncontrolled study. The authors reported no major adverse events and no case needing assisted ventilation. Oxygen desaturation (<95%) occurred in 16 (3%) cases. Four of those patients experienced mild hypoxemia (O_2 saturation <90%). There were no cases of severe hypoxemia (O_2 saturation <85%). The authors reported that all cases were due to upper airway obstruction as a result of propofol-induced hypotonia, and responded to increasing the flow rate of oxygen, jaw lift, and temporary cessation of the propofol infusion. No patient experienced bradycardia, tachycardia, or hypotension.

Heuss *et al.*[27] reported that registered nurses safely administered propofol in 5,178 endoscopies. There were no major adverse events. Among patients with an initial oxygen saturation below 90% (n=43), 3 (7%) suffered a further desaturation greater than 3%. Among patients with an initial oxygen saturation above 90% (n=5126), a drop in oxygen saturation below 85% was found in 28 patients (0.6%). These patients were treated with short (<1 minute) bag ventilation (n=4), positioning of a nasopharyngeal tube (n=9), or spontaneously improved

with supplemental oxygen (n=15) before emergency measures were started. Most of the 31 incidents occurred during esophagogastroduodenoscopy (EGD) (n=26) or in patients with a bronchial carcinoma (n=3). All patients recovered from sedation without sequelae.

Kulling *et al.*[28] reported that nurses under the supervision of endoscopists safely administered propofol sedation to 300 patients. There was no episode of apnea. Oxygen saturation fell below 90% for short periods of time in 11 patients (3.7%). Three patients needed a temporary increase in oxygen delivery. No assisted ventilation was necessary in any patient. The mean blood pressure temporarily decreased below 50 mm Hg in 22 patients (7.3%). Two patients needed a 500 mL infusion of normal saline. The heart rate temporarily fell below 50/min. in 10 patients (3.3%), but without any clinical significance and without any treatment.

Cohen *et al.*[11] reported on the administration of propofol in combination with small doses of a benzodiazepine and an opioid to 819 patients by a registered nurse or medical assistant under the supervision of a gastroenterologist. There were no serious adverse events. The authors reported that blood pressure declined 20 mm Hg or more in 218 (27%) of patients, but intervention for hypotension was not needed in any case. Seventy-five episodes (9%) of sustained oxygen desaturation (O_2 saturation <90% for >30 seconds) led to the use of supplemental oxygen. In all of those cases, oxygen saturation was promptly raised above 90% by using the chin thrust maneuver and supplemental oxygen. No patient needed airway support, endotracheal intubation, or hospitalization.

In a subsequent study, Cohen and coworkers[29] reported on the administration of propofol under the same protocol as in the previous study, to an additional 100 patients undergoing colonoscopy or EGD. Transient oxygen desaturation resulting in a need for supplemental oxygen (O_2 saturation <90% for >30 seconds) occurred once during colonoscopy and once during EGD. Hypotension (a decrease in blood pressure >20 mm Hg) occurred in 41 patients (41%), and bradycardia (pulse <50/min) occurred in 5 patients (5%). All such episodes were transient, and did not lead to administration of a pharmacologic agent or other therapeutic intervention. There were no perforations or deaths, and no patient needed assisted ventilation or hospitalization.

One group has concluded that nurses can administer propofol safely and effectively to high-risk patients. Heuss *et al.*[30] concluded that nurses can administer propofol safely to patients in ASA classes III and IV, as long as the patients are carefully monitored and receive a lower dose of propofol. Nurses gave propofol to 1,370 endoscopy patients in ASA classes III and IV, of whom 642 (47%) were matched with 642 endoscopy patients in ASA classes I and II who also received propofol from nurses. There were no major complications in either group. In the group comprised of patients in classes III and IV, there was a statistically significant increase in the risk of a short oxygen desaturation below 90% (p=0.036). There was no statistically significant difference between the numbers of patients in each group who received a short emergency intervention (n=6 in the ASA III/IV group, n=1 in the ASA I/II group, p=0.124). All patients recovered without sequelae and without a further need for intense

care because of a complication from the sedation. No patient needed intubation, and no perforations occurred. In the 728 nonmatched patients, 4 additional interventions occurred, none with sequelae. The two groups did not show a statistically significant difference in mean decrease of oxygen saturation. The ASA I/II group experienced a significantly greater decrease in arterial blood pressure and heart rate. One episode of bradycardia in each group was treated with atropine.

In a separate report, Heuss and associates[31] concluded that nurses can administer propofol safely to the elderly. Group A (n=1,167) included patients of ages 70 through 85. Group B (n=318) included patients older than 85. The control group (n=2,534) consisted of the records of all patients younger than 70 who were treated with propofol during the same period. There was no sedation-related mortality. Groups A and B did not show a significantly greater need for an emergency intervention than the control group. Compared with the control group, Groups A and B showed a statistically significant increase in the risk of a short oxygen desaturation below 90% and a decrease in oxygen saturation of more than 5%. Arterial hypotension, however, occurred significantly more often in the control group than among Group A or B. There were no adverse effects from the cardiovascular reactions in either Group A or B. There were no statistically significant differences between Groups A and B and the control for mean changes in oxygen saturation, arterial blood pressure, or heart rate.

4. The Warning Is Unwarranted and Should Be Removed from the Propofol Labeling.

The foregoing studies establish that propofol can be administered safely and effectively by medical personnel other than anesthesiologists. The Warning, in its present form, therefore, is no longer warranted, and should be removed from the labeling for propofol.

This labeling change will eliminate the need for an anesthesiologist or nurse anesthetist to participate in endoscopic procedures involving propofol sedation, and thus will reduce the cost to payors of those procedures. The labeling change also will eliminate an unneeded restriction on the practice of gastroenterologists. Removing the Warning, therefore, will advance the principle set forth in Executive Order Number 12,866, 58 FR 51735, that "Federal agencies should promulgate only such regulations as are required by law, are necessary to interpret the law, or are made necessary by compelling public need." To promote that principle, Executive Order 12,866 provides that "[e]ach agency shall tailor its regulations to impose the least burden on society . . . consistent with obtaining the regulatory objectives." Exec. Order No. 12,866, 58 FR 51735. For these reasons, petitioner respectfully requests that the Commissioner grant the proposed labeling change.

C. Environmental Impact

This petition is categorically excluded from the environmental assessment requirement under 21 C.F.R. §§ 25.30 & 25.31 (2005).

D. Economic Impact

Petitioner will provide an economic impact statement upon request by the Commissioner, pursuant to 21 C.F.R. § 10.30(b) (2005).

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.

Respectfully submitted,

WILLIAMS & CONNOLLY LLP

By: _____

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Attorneys for Petitioner American College of Gastroenterology

Attachments

References Cited in Citizen Petition Submitted June 27, 2005
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1. Sipe BW, Rex DK, Latinovich D et al. Propofol versus midazolam/meperidine for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Gastrointest Endosc.* 2002;55:815-825.
2. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol.* 2000;95:1476-1479.
3. Ulmer BJ, Hansen JJ, Overley CA et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol.* 2003;1:425-432.
4. Graber RG. Propofol in the endoscopy suite: an anesthesiologist's perspective. *Gastrointest Endosc.* 1999;49:803-806.
5. Guise PA. Asystole following propofol and fentanyl in an anxious patient. *Anaesth Intensive Care.* 1991;19:116-118.
6. Carlsson U, Grattidge P. Sedation for upper gastrointestinal endoscopy: a comparative study of propofol and midazolam. *Endoscopy.* 1995;27:240-243.
7. Chen SC, Rex DK. Review article: registered nurse-administered propofol sedation for endoscopy. *Aliment Pharmacol Ther.* 2004;19:147-155.
8. Qadeer MA, Vargo JJ, Khandwala F, Zuccaro G. Propofol's safety profile is equivalent to standard sedation with narcotics/benzodiazepines – a meta analysis [abstract]. *Gastroenterology.* 2005; 128:A-288.
9. Qadeer MA, Vargo JJ, Khandwala F, Zuccaro G. Procedure-specific risk of cardiopulmonary complications is same for propofol and traditional sedation: a meta analysis [abstract]. *Gastroenterology.* 2005; 128:A-287.
10. Gangi S, Saidi F, Patel K, Johnstone B, Jaeger J, Shine D. Cardiovascular complications after GI endoscopy: occurrence and risks in a large hospital system. *Gastrointest Endosc.* 2004;60:679-685.
11. Cohen LB, Dubovsky AN, Aisenberg J, Miller KM. Propofol for endoscopic sedation: a protocol for safe and effective administration by the gastroenterologist. *Gastrointest Endosc.* 2003;58:725-732.
12. Meltzer B. RNs pushing propofol. *Outpatient Surg.* 2003;4:24-37.
13. Aisenberg J, Brill JV, Ladabaum U, Cohen LB. Sedation for gastrointestinal endoscopy: new practices, new economics. *Am J Gastroenterol.* 2005;100:996-1000.
14. Bell GD, Charlton JE. Colonoscopy – is sedation necessary and is there any role for intravenous propofol? *Endoscopy.* 2000;32:264-267.
15. Debate: propofol may be safely administered by trained nonanesthesiologists. *Am J Gastroenterol.* 2004;99:1207-1211.
16. Vargo JJ, Eisen GM, Faigel DO, Holub J, Lieberman DA. Anesthesiologist or non-anesthesiologist-administered propofol and cardiopulmonary complications for endoscopy: which is safer? [abstract]. *Gastrointest Endosc.* 2004;59:AB93.
17. Vargo JJ, Zuccaro G, Dumot JA et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology.* 2002;123:8-16.

18. Kongkam P, Pornphisarn B, Rerknimitr R. Non-anesthetist administered propofol for ERCP; efficacy, safety profile and side effect: a prospective randomized trial [abstract]. *Gastrointest Endosc.* 2004;59:AB127.
19. Vargo JJ, Eisen GM, Faigel DO, Holub J, Lieberman DA. Cardiopulmonary complications with non-anesthesiologist-administered propofol vs. standard sedation: the CORI experience [abstract]. *Gastrointest Endosc.* 2004;59:AB132.
20. Walker JA, McIntyre RD, Schleinitz PF et al. Nurse-administered propofol sedation without anesthesia specialists in 9152 endoscopic cases in an ambulatory surgery center. *Am J Gastroenterol.* 2003;98:1744-1750.
21. Rex DK, Overley C, Kinser K et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am J Gastroenterol.* 2002;97:1159-1163.
22. Rex DK, Heuss LT, Walker JA. Nurse administered propofol sedation: safety record among individual nurses and physicians in 3 centers [abstract]. *Am J Gastroenterol.* 2004;99:S300.
23. Tohda G, Higashi S, Sakumoto H, Sumiyoshi K, Kane T. Propofol sedation during endoscopic procedures: safety and effective administration by registered nurses, supervised by endoscopists [abstract]. *Gastrointest Endosc.* 2005;61:AB123.
24. Baptista A, Bonilla Y, Bronstein M et al. Propofol sedation for gastrointestinal endoscopy administered by nursing staff under gastroenterologist supervision [abstract]. *Gastrointest Endosc.* 2005;61:AB108.
25. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: a prospective observational study of more than 2000 cases. *Gastrointest Endosc.* 2003;57:664-671.
26. Yusoff I, Raymond G, Sahai AV. Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. *Gastrointest Endosc.* 2004;60:356-360.
27. Heuss LT, Schnieper P, Pflimlin E, Beglinger C. Nurse-administered sedation with propofol under observation of the endoscopist: a prospective observation study with more than 5000 patients [abstract]. *Gastrointest Endosc.* 2003;57:AB105.
28. Külling D, Rothenbühler R, Inauen W. Safety of nonanesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. *Endoscopy.* 2003;35:679-682.
29. Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc.* 2004;59:795-803.
30. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients—a prospective, controlled study. *Am J Gastroenterol.* 2003;98:1751-1757.
31. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Conscious sedation with propofol in elderly patients: a prospective evaluation. *Aliment Pharmacol Ther.* 2003;17:1493-1501.

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June 27, 2005

By Federal Express

Division of Dockets Management
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Re: Citizen Petition

Dear Sir or Madam:

Enclosed for filing are an original and three copies of a citizen petition, including an appendix, that we submit on behalf of the American College of Gastroenterology.

Thank you very much for your assistance.

Very truly yours,

Michael K. Stern

Enclosures

APPENDIX

References Cited in Citizen Petition Submitted June 27, 2005
by Williams & Connolly LLP
on behalf of the American College of Gastroenterology

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2. Koshy G, Nair S, Norkus EP, Hertan HI, Pitchumoni CS. Propofol versus midazolam and meperidine for conscious sedation in GI endoscopy. *Am J Gastroenterol.* 2000;95:1476-1479.
3. Ulmer BJ, Hansen JJ, Overley CA et al. Propofol versus midazolam/fentanyl for outpatient colonoscopy: administration by nurses supervised by endoscopists. *Clin Gastroenterol Hepatol.* 2003;1:425-432.
4. Graber RG. Propofol in the endoscopy suite: an anesthesiologist's perspective. *Gastrointest Endosc.* 1999;49:803-806.
5. Guise PA. Asystole following propofol and fentanyl in an anxious patient. *Anaesth Intensive Care.* 1991;19:116-118.
6. Carlsson U, Grattidge P. Sedation for upper gastrointestinal endoscopy: a comparative study of propofol and midazolam. *Endoscopy.* 1995;27:240-243.
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8. Qadeer MA, Vargo JJ, Khandwala F, Zuccaro G. Propofol's safety profile is equivalent to standard sedation with narcotics/benzodiazepines – a meta analysis [abstract]. *Gastroenterology.* 2005; 128:A-288.
9. Qadeer MA, Vargo JJ, Khandwala F, Zuccaro G. Procedure-specific risk of cardiopulmonary complications is same for propofol and traditional sedation: a meta analysis [abstract]. *Gastroenterology.* 2005; 128:A-287.
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11. Cohen LB, Dubovsky AN, Aisenberg J, Miller KM. Propofol for endoscopic sedation: a protocol for safe and effective administration by the gastroenterologist. *Gastrointest Endosc.* 2003;58:725-732.
12. Meltzer B. RNs pushing propofol. *Outpatient Surg.* 2003;4:24-37.
13. Aisenberg J, Brill JV, Ladabaum U, Cohen LB. Sedation for gastrointestinal endoscopy: new practices, new economics. *Am J Gastroenterol.* 2005;100:996-1000.
14. Bell GD, Charlton JE. Colonoscopy – is sedation necessary and is there any role for intravenous propofol? *Endoscopy.* 2000;32:264-267.
15. Debate: propofol may be safely administered by trained nonanesthesiologists. *Am J Gastroenterol.* 2004;99:1207-1211.
16. Vargo JJ, Eisen GM, Faigel DO, Holub J, Lieberman DA. Anesthesiologist or non-anesthesiologist-administered propofol and cardiopulmonary complications for endoscopy: which is safer? [abstract]. *Gastrointest Endosc.* 2004;59:AB93.
17. Vargo JJ, Zuccaro G, Dumot JA et al. Gastroenterologist-administered propofol versus meperidine and midazolam for advanced upper endoscopy: a prospective, randomized trial. *Gastroenterology.* 2002;123:8-16.

18. Kongkam P, Pornphisarn B, Rerknimitr R. Non-anesthetist administered propofol for ERCP; efficacy, safety profile and side effect: a prospective randomized trial [abstract]. *Gastrointest Endosc.* 2004;59:AB127.
19. Vargo JJ, Eisen GM, Faigel DO, Holub J, Lieberman DA. Cardiopulmonary complications with non-anesthesiologist-administered propofol vs. standard sedation: the CORI experience [abstract]. *Gastrointest Endosc.* 2004;59:AB132.
20. Walker JA, McIntyre RD, Schleinitz PF et al. Nurse-administered propofol sedation without anesthesia specialists in 9152 endoscopic cases in an ambulatory surgery center. *Am J Gastroenterol.* 2003;98:1744-1750.
21. Rex DK, Overley C, Kinser K et al. Safety of propofol administered by registered nurses with gastroenterologist supervision in 2000 endoscopic cases. *Am J Gastroenterol.* 2002;97:1159-1163.
22. Rex DK, Heuss LT, Walker JA. Nurse administered propofol sedation: safety record among individual nurses and physicians in 3 centers [abstract]. *Am J Gastroenterol.* 2004;99:S300.
23. Tohda G, Higashi S, Sakumoto H, Sumiyoshi K, Kane T. Propofol sedation during endoscopic procedures: safety and effective administration by registered nurses, supervised by endoscopists [abstract]. *Gastrointest Endosc.* 2005;61:AB123.
24. Baptista A, Bonilla Y, Bronstein M et al. Propofol sedation for gastrointestinal endoscopy administered by nursing staff under gastroenterologist supervision [abstract]. *Gastrointest Endosc.* 2005;61:AB108.
25. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Risk stratification and safe administration of propofol by registered nurses supervised by the gastroenterologist: a prospective observational study of more than 2000 cases. *Gastrointest Endosc.* 2003;57:664-671.
26. Yusoff I, Raymond G, Sahai AV. Endoscopist administered propofol for upper-GI EUS is safe and effective: a prospective study in 500 patients. *Gastrointest Endosc.* 2004;60:356-360.
27. Heuss LT, Schnieper P, Pflimlin E, Beglinger C. Nurse-administered sedation with propofol under observation of the endoscopist: a prospective observation study with more than 5000 patients [abstract]. *Gastrointest Endosc.* 2003;57:AB105.
28. Külling D, Rothenbühler R, Inauen W. Safety of nonanesthetist sedation with propofol for outpatient colonoscopy and esophagogastroduodenoscopy. *Endoscopy.* 2003;35:679-682.
29. Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J. Moderate level sedation during endoscopy: a prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc.* 2004;59:795-803.
30. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Safety of propofol for conscious sedation during endoscopic procedures in high-risk patients—a prospective, controlled study. *Am J Gastroenterol.* 2003;98:1751-1757.
31. Heuss LT, Schnieper P, Drewe J, Pflimlin E, Beglinger C. Conscious sedation with propofol in elderly patients: a prospective evaluation. *Aliment Pharmacol Ther.* 2003;17:1493-1501.